Spastic paraplegia type 5A

Spastic paraplegia type 5A is one of a group of genetic disorders known as hereditary spastic paraplegias. These disorders are characterized by muscle stiffness (spasticity) and severe weakness in the lower limbs (paraplegia). Hereditary spastic paraplegias are often divided into two types: pure and complex. The pure types involve spasticity and weakness only in the lower limbs, while the complex types involve additional problems with other areas of the body; additional features can include changes in vision, changes in intellectual functioning, brain abnormalities, and disturbances in nerve function (neuropathy). Spastic paraplegia type 5A is usually a pure hereditary spastic paraplegia, although complex type features have been reported in some individuals, usually in those who have had the condition for many years.

In addition to spasticity and weakness, people with spastic paraplegia type 5A can lose the ability to sense the position of their limbs or detect vibrations with their lower limbs. They may also have muscle wasting (amyotrophy), reduced bladder control, or high arches of the feet (pes cavus). The signs and symptoms of spastic paraplegia type 5A usually appear in adolescence but can begin at any time between infancy and mid-adulthood. The condition slowly worsens over time, often leading affected individuals to require walking support or wheelchair assistance.

Frequency

Spastic paraplegia type 5A is a rare condition. Its prevalence is unknown.

Causes

Spastic paraplegia type 5A is caused by mutations in the *CYP7B1* gene. This gene provides instructions for making an enzyme called oxysterol 7-alpha-hydroxylase. In the brain, oxysterol 7-alpha-hydroxylase is involved in a pathway that converts cholesterol to hormones called neurosteroids. These neurosteroids increase nerve cell activity (excitability) and promote cell survival and communication between nerve cells. Oxysterol 7-alpha-hydroxylase helps maintain normal cholesterol levels in the brain and, by producing neurosteroids through altering existing hormones within the pathway, regulates the effects of neurosteroids on the brain.

CYP7B1 gene mutations that cause spastic paraplegia type 5A reduce or eliminate the activity of oxysterol 7-alpha-hydroxylase. In the brain, a decrease in enzyme activity results in an accumulation of cholesterol and alters neurosteroid production triggered by oxysterol 7-alpha-hydroxylase. Abnormal levels of neurosteroids impairs cell survival, likely leading to nerve cell death. The abnormal buildup of cholesterol in the brain probably also contributes to the death of nerve cells. The loss of these cells results in the deterioration of nervous system functions (neurodegeneration) and causes the

movement problems, weakness, and other signs and symptoms of spastic paraplegia type 5A.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- autosomal recessive spastic paraplegia 5A
- spastic paraplegia 5A
- SPG5A

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting
- Gasser T, Finsterer J, Baets J, Van Broeckhoven C, Di Donato S, Fontaine B, De Jonghe P, Lossos A, Lynch T, Mariotti C, Schöls L, Spinazzola A, Szolnoki Z, Tabrizi SJ, Tallaksen CM, Zeviani M, Burgunder JM, Harbo HF; EFNS. EFNS guidelines on the molecular diagnosis of ataxias and spastic paraplegias. Eur J Neurol. 2010 Feb;17(2):179-88. doi: 10.1111/j.1468-1331.2009.02873.x. Epub 2009 Dec 28.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20050888
- Genetic Testing Registry: Hereditary spastic paraplegia 5A
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1849115/

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22spastic+paraplegia+type+5A%22+OR+%22Spastic+Paraplegia%2C+Hereditary%22

Other Diagnosis and Management Resources

- GeneReview: Hereditary Spastic Paraplegia Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1509
- Spastic Paraplegia Foundation, Inc.: Treatments and Therapies
  https://sp-foundation.org/understanding-pls-hsp/treatments.html

Additional Information & Resources

Health Information from MedlinePlus

- Health Topic: Neurologic Diseases
  https://medlineplus.gov/neurologicdiseases.html
- Health Topic: Neuromuscular Disorders
  https://medlineplus.gov/neuromusculardisorders.html
- Health Topic: Paralysis
  https://medlineplus.gov/paralysis.html

Genetic and Rare Diseases Information Center

- Hereditary spastic paraplegia
  https://rarediseases.info.nih.gov/diseases/6637/hereditary-spastic-paraplegia
- Spastic paraplegia 5A
  https://rarediseases.info.nih.gov/diseases/4926/spastic-paraplegia-5a

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Hereditary Spastic Paraplegia Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Hereditary-spastic-paraplegia-Information-Page

Educational Resources

- MalaCards: spastic paraplegia 5a, autosomal recessive
  https://www.malacards.org/card/spastic_paraplegia_5a_autosomal_recessive
- Merck Manual Consumer Version
  https://www.merckmanuals.com/home/brain,-spinal-cord,-and-nerve-disorders/spinal-cord-disorders/hereditary-spastic-paraparesis
- National Health Service (UK)
  https://www.nhs.uk/conditions/hereditary-spastic-paraplegia/
- Orphanet: Autosomal recessive spastic paraplegia type 5A
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=100986

Patient Support and Advocacy Resources

- Contact a Family (UK)
  https://contact.org.uk/advice-and-support/health-medical-information/conditions/f/familial-spastic-paraplegia/
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/hereditary-spastic-paraplegia/
- RareConnect
  https://www.rareconnect.org/en/community/hereditary-spastic-paraplegia

Clinical Information from GeneReviews

- Hereditary Spastic Paraplegia Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1509

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28spastic+paraplegia+type+5A%5BALL%5D%29+OR+%28SPG5A%5BALL%5D%29+OR+%28spastic+paraplegia+5A%5BALL%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- SPASTIC PARAPLEGIA 5A, AUTOSOMAL RECESSIVE
  http://omim.org/entry/270800

Medical Genetics Database from MedGen

- Hereditary spastic paraplegia 5A
  https://www.ncbi.nlm.nih.gov/medgen/376521

Sources for This Summary

- Arnoldi A, Crimella C, Tenderini E, Martinuzzi A, D'Angelo MG, Musumeci O, Toscano A, Scarlato M, Fantin M, Bresolin N, Bassi MT. Clinical phenotype variability in patients with hereditary spastic paraplegia type 5 associated with CYP7B1 mutations. Clin Genet. 2012 Feb;81(2):150-7. doi: 10.1111/j.1399-0004.2011.01624.x. Epub 2011 Jan 31.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21214876
- Criscuolo C, Filla A, Coppola G, Rinaldi C, Carbone R, Pinto S, Wang Q, de Leva MF, Salvatore E, Banfi S, Brunetti A, Quarantelli M, Geschwind DH, Pappatà S, De Michele G. Two novel CYP7B1 mutations in Italian families with SPG5: a clinical and genetic study. J Neurol. 2009 Aug;256(8):1252-7. doi: 10.1007/s00415-009-5109-3. Epub 2009 Apr 12.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19363635

- Goizet C, Boukhris A, Durr A, Beetz C, Truchetto J, Tesson C, Tsaousidou M, Forlani S, Guyant-Maréchal L, Fontaine B, Guimarães J, Isidor B, Chazouillères O, Wendum D, Grid D, Chevy F, Chinnery PF, Coutinho P, Azulay JP, Feki I, Mochel F, Wolf C, Mhiri C, Crosby A, Brice A, Stevanin G. CYP7B1 mutations in pure and complex forms of hereditary spastic paraplegia type 5. Brain. 2009 Jun;132(Pt 6):1589-600. doi: 10.1093/brain/awp073. Epub 2009 May 12.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19439420
- Lan MY, Yeh TH, Chang YY, Kuo HC, Sun HS, Lai SC, Lu CS. Clinical and genetic analysis of Taiwanese patients with hereditary spastic paraplegia type 5. Eur J Neurol. 2015 Jan;22(1):211-4. doi: 10.1111/ene.12407. Epub 2014 Mar 18.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24641183
- Tsaousidou MK, Ouahchi K, Warner TT, Yang Y, Simpson MA, Laing NG, Wilkinson PA, Madrid RE, Patel H, Hentati F, Patton MA, Hentati A, Lamont PJ, Siddique T, Crosby AH. Sequence alterations within CYP7B1 implicate defective cholesterol homeostasis in motor-neuron degeneration. Am J Hum Genet. 2008 Feb;82(2):510-5. doi: 10.1016/j.ajhg.2007.10.001. Epub 2008 Jan 18.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18252231
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2426914/

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